Application No. 10/762,964
Filed: January 22, 2004
TC Art Unit: 1618
Confirmation No.: 6339

REMARKS

Claims 1-18 are pending. Claims 1-10 and 12-18 are rejected. Claim 11 is objected to, and is noted as being allowable except for its dependency on a rejected base claim.

Applicant notes that while the Office Action Summary includes claims 17 and 18 among the rejected claims, none of the individual rejections in the body of the Office Action includes either claim 17 or claim 18. Clarification is requested.

Claim 1 is amended herein to reword the claim for clarity. The previous "if" clause has been replaced with a more typical "wherein" clause to more clearly specify the ionic dispersant content of the solid formulation. No new matter has been added.

Claims 1-10 and 12-18 are rejected for alleged anticipation or obviousness. The claim rejections are respectfully traversed. In view of the amendments and the arguments below, all claims are believed to be allowable, and reconsideration of the rejections is hereby requested.

Interview

Applicant thanks the Examiner for the courtesy of the interview on July 10, 2007. During the interview, the present amendment of claim 1 was discussed, as were the teachings of the Brown reference with regard to flocculants.

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Rejection Under 35 U.S.C. 102(b)

Claims 1-4, 6-8, and 10 are rejected for alleged anticipation by Brown U.S. 3,236,735. Brown is cited as teaching solid formulations comprising barium sulfate and a flocculant. The distinction previously argued by Applicant regarding the low content of ionic dispersants required by the present claims was not given weight, because this was considered merely optional in view of the claim term "if".

Claim 1 has been amended to recite a solid stool marker formulation "wherein upon dilution of said solid stool marker formulation to provide 0.5 to 3% w/v barium sulfate, from 0 to less than 0.035N ionic dispersants are present". Thus, claim 1 as amended is clear in requiring the solid formulation to have at most a very low content of ionic dispersants. As argued previously, this alone should be sufficient to distinguish the claimed composition over the Brown compositions, which employ sufficient anionic dispersants to achieve barium distribution along the lining of the colon. The compositions of the present claims, however, limit the amount of anionic dispersants, and require sufficient flocculant, so that the barium is concentrated in the stool and serves as a stool marker, not a marker for the lining of the colon.

The Office Action argues that "[w]hether or not the claimed compositions cause barium sulfate to be dispersed or flocculated is not relevant, only what is contained in the compositions may be used to distinguish over the prior art." Office Action at page 3, lines 20-22. However, in this case, the chemical composition of the claimed formulation is different from the chemical composition

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of the Brown formulations because the different uses of the respective formulations requires it. The overall action of the formulations as either flocculating or dispersive necessarily drives different chemical compositions.

There are at least two differences in chemical composition between the Brown formulations and the formulations of the present claims. First, Brown uses an amount of anionic dispersant that is higher than recited by the present claims, as discussed above. And second, Brown does not teach or suggest the use of a flocculant in an amount required by the present claims, as discussed below.

Brown teaches the use of bentonite in barium sulfate compositions, but not as a flocculant. He teaches bentonite, especially combined with a dispersant such as sodium carboxymethylcellulose (CMC), as an anti-settling agent or an anti-caking agent. In fact, Brown specifically teaches away from using bentonite alone (i.e., without a dispersant) or in an amount that would cause flocculation in the intestine:

> The sodium CMC also enhances the effectiveness of bentonite as an anti-settling and anti-caking agent. Bentonite is a useful suspending agent for barium sulfate to retard settling of the barium sulfate prior to its administration. Unfortunately, it is not compatible with gastric secretions, and used alone or in large quantities it will increase flocculation of the barium sulfate in the intestine.

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Brown at column 4, lines 51-57. Furthermore, the only specific formulation taught by Brown which includes bentonite is a liquid formulation (see Example 3 of Brown), in which case bentonite is used as an anti-settling agent in a dispersive formulation ("provides excellent coating of the colon") that includes sodium CMC as a dispersant.

It is further noted that in Brown's Example 3, all of the components are dissolved in water prior to adding the barium sulfate, which is "incorporated rapidly." One of the components, the antifoaming agent, is added from a commercially available stock solution. It is unclear what result would obtain if all of the components, including barium sulfate, were mixed as solids and then water was added prior to administering the mixture to a subject. The result could well be an unstable or unsuitable suspension. Thus, Example 3 is not an enabling disclosure for a solid formulation having the same components as in the example, but in solid instead of liquid form.

In contrast to Brown's dispersive formulations, the present claims require a solid formulation that will lead to flocculation in the intestine by virtue of reciting: "wherein 0.25 g of said solid stool marker formulation diluted with water to 50ml and titrated against 3.0% w/v ferrous sulfate at pH 5.0-5.5 has a flocculation resistance of less than 5ml." The relevance of the flocculation resistance value is not a mere assertion; it is demonstrated by data summarized in Table 1 of the present specification. Of the formulations for which results are shown in Table 1, only Formulas II and III had a flocculation resistance value of 5.0 ml or greater, i.e., outside the range of present

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claim 1. And only Formulas II and III performed poorly as stool markers, producing a performance score as a stool marker of less than 5 out of a perfect score of 10. All the remaining formulas (I, IV, V, and VI) had flocculation resistance values less than 5 ml and performance scores between 5 and 10. The Brown formulas which provided "excellent coating of the colon" clearly would not have yielded performance scores in the range of 5-10 as stool markers.

Brown does not disclose a solid stool marker formulation comprising barium sulfate and a flocculant, wherein upon dilution of said solid stool marker formulation to provide 0.5 to 3% w/v barium sulfate, from 0 to less than 0.035N ionic dispersants are present, and wherein 0.25 g of said solid stool marker formulation diluted with water to 50ml and titrated against 3.0% w/v ferrous sulfate at pH 5.0-5.5 has a flocculation resistance of less than 5ml; therefore, Brown does not anticipate any of the present claims. Withdrawal of this rejection is respectfully requested.

Rejections Under 35 U.S.C. 103(a)

Claims 1-4, 6-8, and 10-16 are rejected as allegedly obvious over Brown U.S. 3,236,735 in view of Queille U.S. 4,120,946. Brown is cited for the teachings described above, and Queille is cited for teaching a formulation including barium sulfate, xanthan gum, and citrate.

The Office Action acknowledges that the combination of Brown and Queille fails to teach the formulation of claim 11, containing barium sulfate, clay, xanthan gum, and citrate; however the rejection has been maintained with respect to composition claims

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1-4, 6-8, and 10. Neither the present Office Action nor the previous one offered any explanation of what Queille offers in addition to Brown with respect to any of claims 1-4, 6-8, 10 and 12-16.

The point of the Queille invention was "to provide pharmaceutical compositions for barium opacification of the digestive tract which are characterized by the fact they contain colloidal barium sulfate and a polyacrylamide in an aqueous vehicle." Queille at column 1, lines 57-61. Queille discloses only liquid (aqueous) formulations, not solid formulations. Queille also uses polyacrylamide as a suspension agent for barium and to promote the adherence of barium to the walls of the colon. Queille at column 2,lines 11-16. The Queille compositions are thus dispersive and not flocculating. As discussed above, Brown fails to teach or suggest a flocculating formulation of barium sulfate having at most a very low anionic dispersant content, as recited by claim 1.

Therefore, neither Brown nor Queille, either alone or in combination, teaches or suggests a solid stool marker formulation comprising barium sulfate and a flocculant, wherein upon dilution of said solid stool marker formulation to provide 0.5 to 3% w/v barium sulfate, from 0 to less than 0.035N ionic dispersants are present, and wherein 0.25 g of said solid stool marker formulation diluted with water to 50ml and titrated against 3.0% w/v ferrous sulfate at pH 5.0-5.5 has a flocculation resistance of less than 5ml. Claims 1-4, 6-8, and 10-16 are not obvious over Brown in view of Queille, and withdrawal of this rejection is respectfully requested.

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Claims 1-10 and 12-16 are rejected as allegedly obvious over Brown U.S. 3,236,735 in view of Ruddy U.S. 5,466,440 and Weaver U.S. 3,935,099. The Office Action rejects Applicant's previous argument with respect to this rejection by stating that "Ruddy was used to show that barium sulfate having particle sizes within the claimed range and prepared via high shear is known in the art for imaging." Furthermore, the Office Action points out that Ruddy's composition appear not to require ionic dispersants, because they require only barium sulfate, a bioadhesive surfactant, a clay, and water. The Office Action also seems to imply that Weaver is cited merely to reach claim 9, which recites a formulation treated with sonication; the citation of Weaver also appears to relate to the interpretation that claim 1, as previously worded, was a product by process claim.

There are several distinctions between the formulations taught by Ruddy and the present claims. First, Ruddy teaches only liquid formulations, as stated in the Office Action and in Ruddy at column 3, line 67. Second, the Ruddy formulations include a bioadhesive surfactant. While the surfactant may be uncharged, it is nevertheless a dispersant and has "mucoadhesive properties," meaning that it has the ability to disperse barium sulfate within the gastrointestinal tract and adhere it to the mucosal lining. The inclusion of a surfactant with mucoadhesive properties is inconsistent with a formulation having an ability to flocculate barium sulfate and to serve as a stool marker. The inclusion of clay in the Ruddy formulations, together with a surfactant, is exactly analogous to Brown's use of bentonite together with an

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anionic dispersant. The clay is required as a suspending agent for barium sulfate, while either a nonionic surfactant or an ionic dispersant prevents the very flocculation which is required by the present claims and required for the formulation to function as a stool marker as opposed to a contrast agent for the colonic mucosal lining.

Even if the use of high shear as disclosed in Ruddy, or sonication as disclosed in Weaver, were relevant to some of the dependent claims, the combined teachings of Brown, Ruddy, and Weaver still does not teach or suggest the invention of claim 1 because the references, either singly or combined, fail to teach a solid barium sulfate formulation that would meet the flocculation resistance value which is required by all of the present claims. The withdrawal of this rejection is respectfully requested.

Claims 1-4, 6-8, 10, and 12-16 are rejected as allegedly obvious over Brown U.S. 3,236,735 in view of Kaufman U.S. 6,331,116. The Office Action rejects Applicant's previous argument of this rejection on the basis that the former "if" language of claim 1 was not effective as a limitation for the solid formulation. As the amendment of claim 1 should clarify, the solid formulation of claim 1 differs from Brown, as discussed above, and from Kaufman, which merely teaches virtual colonoscopy using a prior art barium sulfate solution but fails to teach or even suggest the use of a flocculant. Therefore, the Brown and Kaufman references, either singly or combined, fail to teach or suggest every limitation of the present claims, and fail to render the claims obvious. The withdrawal of the rejection is respectfully requested.

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The Examiner is encouraged to telephone the undersigned attorney to discuss any matter which would expedite allowance of the present application.

Respectfully submitted,

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